

Distinct molecular mechanisms for development of brain asymmetries?

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Abstract

Brain and behavioral asymmetries are often associated with neurodevelopmental disorders, but have yet uncovered genetic and developmental mechanisms. A recent study by Vingerhoets and colleagues (2018), published in *Brain Structure and Function*, examined neural structural and functional asymmetries in a cohort of patients with situs inversus totalis, with and without primary ciliary dyskinesia as a second diagnosis. The authors showed a potential for independent randomization of handedness, language dominance, and visceral laterality; this provides the first experimental hint that different mechanisms for symmetry breaking and molecular cascades may be involved in producing asymmetry of body and brain.

Keywords: brain left-right structural asymmetry, situs viscerum inversus totalis, primary ciliary dyskinesia, handedness, language dominance, developmental mechanisms, neurodevelopmental diseases.

Some neurodevelopmental disorders of complex or unknown etiology such as schizophrenia, autism spectrum disorder, and speech and language disorders are often associated with an impaired development of functional and structural brain asymmetry (Crow, Done, and Sacker, 1996; Petty, 1999; Robichon, Levrier, Farnarier, and Habib, 2000; Herbert et al., 2005). The direction of the causative link between a somewhat abnormal (reduced or even reversed) brain asymmetry and the diseases is, however, poorly understood. It is unclear whether disruption of normal functional and structural brain asymmetry is a by-product of a disease, or vice versa — differential disruption of brain asymmetry may cause a spectrum of neurodevelopmental abnormalities that are classified as different syndromes. A lack of clear understanding of the genetic background and developmental mechanisms of the phenomena (brain asymmetry and psychosis/dyslexia) complicates the situation (for more discussion, see: Levchenko, Davtian, Petrova, and Malashichev, 2014). The well-known cascades of asymmetrically-expressed genes with the *Nodal* in the center of the network, which are responsible for the formation of normal situs of internal organs in vertebrates, are not necessarily all the same as those involved in formation of normal brain asymmetry (Malashichev and Wassersug, 2004; Malashichev, 2006; Sun and Walsh, 2006). Particularly, individuals with situs viscerum inversus do not always show a reversal of brain, handedness, and other behavioral left-right asymmetries. A recent study (Vingerhoets et al., 2018) adds important experimental evidence in support of the existence of distinct mechanisms for development of brain and visceral asymmetries, providing potential insights also into the relationship between them and neurodevelopmental disorders.

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A central role in the transduction of signals and determination of the visceral asymmetries in the vertebral body belongs to a left-sided nodal flow, which is due to ciliary beating at the node during the embryonic neurula stage. The structure of beating cilia in the node lacks the central pair of microtubules (primary cilia) and has a rotational type of movement, and this rotation produces a left-sided nodal flow. Not surprisingly, ciliopathies are sometimes, but not always, accompanied by situs inversus viscerum as a consequence of disrupted primary cilia beating (Davis and Katsanis, 2012; Trulioff, Ermakov, and Malashichev, 2017). On the other hand, proteins associated with the primary cilia may be involved in neurodevelopmental pathogenesis — e.g., *Disc1*, *PCM-1* and *AHI1* are linked to schizophrenia; *TSC1*—to autism; *PCNT*, *DCDC2* and *Dyx1c1*—to dyslexia (see for review: Trulioff, Ermakov, and Malashichev, 2017). Therefore, it would be very important to know whether individuals with the visceral organ situs inversus, who do not show reversal of behavioral handedness, indeed develop visceral reversal due to ciliary dyskinesia. Fortunately, this has recently been tested.

Vingerhoets and colleagues (2018) examined brain structural and functional asymmetries in a cohort of 15 individuals with complete visceral reversal (situs inversus totalis) and found different asymmetry patterns between participants who had ($n = 6$) and didn't have ($n = 9$) primary ciliary dyskinesia (PCD, or Kartagener syndrome) as a second diagnosis. In the former subgroup, language lateralization and posterior lobar asymmetry were not affected by visceral inversion; but in the latter subgroup, which showed default language dominance, five out of nine participants were unexpectedly left-handed. Moreover, frontal and occipital lobe petalia torque was only significantly reversed in the subgroup of situs inversus PCD-unrelated individuals. These findings, above all, indirectly support a long-standing opinion of a link between petalia asymmetry and handedness (Lemay and Kido, 1978), but not language dominance. Although Vingerhoets and colleagues (2018) make all the precautions in their conclusions due to a relatively small sample size, it is actually the first experimental evidence explicitly showing (1) that it is unlikely that ciliary movements play a role in the genesis of human brain laterality, and (2) that visceral laterality, brain torque and language dominance may indeed rely on different developmental mechanisms (for more discussion, see: Malashichev and Wassersug, 2004; Malashichev, 2006). These findings can be further supported by earlier evidence of only partial reversal of behaviors in *fsi* (*frequent situs inversus*) mutant zebrafish (Barth et al., 2005).

These observations and conclusions may have further important consequences for our understanding of abnormal brain development. Indeed, different molecular cascades may regulate not only physiological and

structural asymmetries of the brain; the same may be true for neurodevelopmental disorders, e.g., schizophrenia. Recently, we performed a literature survey trying to demonstrate some linkage between ciliary proteins and neurodevelopmental disorders (schizophrenia, autism, dyslexia) based on involvement of primary cilia in the development of brain asymmetry. However, we failed to find any evidence to confirm this hypothesis (Trulioff, Ermakov, and Malashichev, 2017). It seems that broken ciliary proteins affect brain development via neuronal migration, neuritis outgrowth, or interneuron signaling, etc., but not in a way somehow affecting normal functional brain asymmetries. Hence, it is suggestive that those psychotic patients that have broken primary cilia may have less dysfunction in the asymmetry of the brain and a somewhat different clinical course. In contrast, patients with schizophrenia/autism/dyslexia symptoms that demonstrate a stronger disruption of normal functional brain asymmetry may bear mutations in genes that somehow regulate the latter. One good candidate for this is the WNT/ β -catenin signaling pathway, which is involved both in pathogenesis of, for example, schizophrenia (Singh, 2013; Levchenko et al., 2015) and formation of normal brain asymmetry (Husken and Carl, 2013). Altogether, the study by Vingerhoets and colleagues (2018) may change our conventional thinking that brain and body asymmetry is linked to one or few simple mechanisms, and that those are evidently more diverse and complicated than we previously thought. The same may apply to pathogeneses of neurodevelopmental disorders.

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